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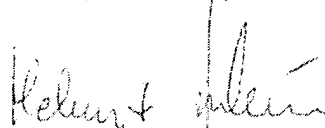
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## Affidavit of Accuracy

I, Helmut Froboese, of Accurapid – The Language Service, hereby certify that the attached translation from Spanish to English of Patent Application No. ES 2 209 649, with an application date of December 9, 2002, published June 16, 2004, entitled PRODUCTO DE HIGIENE BUCODENTAL PARA USO HUMANO Y VETERINARIO A BASE DE MELATONINA COMO PRODUCTO ACTIVO [ORAL HYGIENE PRODUCT FOR HUMAN AND ANIMAL USE WITH A MELATONIN BASE AS AN ACTIVE PRODUCT] was performed by Accurapid – The Language Service. I also certify that our editor, who is a competent translator in the Spanish and English languages, carefully compared the translation to the original, and has informed me that, to the best of his knowledge and belief, the translation is accurate.

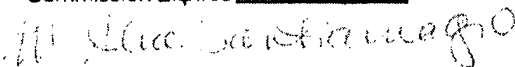
Poughkeepsie, January 11, 2008



Helmut Froboese

State of New York  
County of Dutchess  
Sworn before me on this  
11<sup>th</sup> Day of January, 2008

**M. ALICE SANTIAMAGRO**  
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Commission Expires 12-22-2011



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(19) [symbol] SPANISH PATENT AND TRADEMARK OFFICE  SPAIN	(11) Publication number: <b>2 209 649</b> (21) Application No. 200202810 (51) Int. Cl. <sup>7</sup> : <b>A61K 31/4045</b> A61K 7/16 A61K 38/22 A32K 1/165
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(12)

PATENT APPLICATION

A1

(22) Filing date: <b>12/09/2002</b>	(71) Applicant(s): <b>Carlos Arana Molina</b> (25% assignee) <b>c/ Monachil 4-3</b> <b>18007 Granada, Spain</b> <b>Antonio Cutando Soriano</b> (25% assignee), <b>Darío Acuña Castroviejo</b> (25% assignee) and <b>Gerardo Gómez Moreno</b> (25% assignee)
(43) Date of publication of application: <b>6/16/2004</b>	(72) Inventor(s): <b>Cutando Soriano, Antonio;</b> <b>Acuña Castroviejo, Darío;</b> <b>Gómez Moreno, Gerardo and</b> <b>Villalba Moreno, Juan</b>
(43) Publication date of application brochure: <b>6/16/2004</b>	(74) Agent: <b>Gonzálvez Crespo, Carmen</b>

(54) Title: **Oral hygiene product for human and animal use with a melatonin base as an active product.**

(57) Abstract:

Use of melatonin for human and animal oral hygiene as an active product using hydrophilic and hydrophobic bases or excipients, capable of being used in the preparation of a toothpaste and/or mouthwash in master formulation and in industrial preparation, including melatonin in a proportion of 0.1% to 5% in toothpastes and/or mouthwashes, as well as in animal feed, including an antioxidant active at low concentration and in a wide pH range to prevent autooxidation of melatonin.

**ES 2 209 649 A1**

Sale of fascicles: Spanish Patent and Trademark Office. C/Panama, 1 – 28036 Madrid

## **DESCRIPTION**

Use of melatonin for human and animal oral hygiene as an active product.

### **Object of the invention**

[0001] This description relates to a patent application for utilization of melatonin for human and animal oral hygiene as an active product, for human or animal use, using the antioxidant and immuno-stimulating activity of this compound.

[0002] When it is to be used on humans, it is constituted as a toothpaste or mouthwash, whereas when it is to be used as a product for animal use, the melatonin effects will be taken advantage of by including said compound in food pellets.

### **Scope of the invention**

[0003] This invention is to be used in the industry manufacturing human and animal oral hygiene products.

### **Background of the invention**

[0004] All physiological processes depend on the capacity of cells to receive nutrients and eliminate waste products to the extracellular space, and during these processes free radicals are generated. Free radical production significantly increases in the case of any illness or lesion.

[0005] Free radicals formed in this way are classified into two groups, i.e.:

- Free oxygen radicals and
- Free nitrogen radicals

[0006] The former, constituted as free oxygen radicals, are derived from the incomplete reduction of oxygen with the aid of the superoxide anion and the highly toxic hydroxyl radical.

[0007] Among the latter, specifically the free nitrogen radicals, are nitric oxide (NO) and the peroxyxynitrites, which are very toxic and derived from the reaction between nitric oxide and the superoxide anion.

[0008] Nitric oxide is in turn produced by nitric oxide synthase (NOS), of which there are at least three isoforms and, although under basal conditions there are limited and controlled of nitric oxide [sic], under the effects of inflammatory processes, the expression of the inducible isoform of nitric oxide synthase (NOS) increases, generating very large quantities of nitric oxide.

[0009] Under these conditions, levels of free oxygen and nitrogen radicals are very high, inducing cell damage and death and also favoring or obtaining an increase in the production of free radicals that generate an increase in the rigidity of cell membranes and connective tissue due to crossed links. This causes a decrease in blood supply to the organs and tissues with the consequent decrease in tissue perfusion. To counteract the accumulation of “cytotoxic bioproducts” [*Translator*: may have meant “cytotoxic byproducts”] derived from the oxidative reactions necessary for life, living organisms have developed detoxification and DNA repair processes and natural antioxidants, as well as free radical purging agents, enzymes, and protein degradation systems.

[0010] Intracellular purging activity includes the production (probably under genetic control) of various antioxidants in response to the oxidative reactions. In these systems it is noted that they are sufficient to give cellular protection, but not to produce toxic effects by their own antioxidant activity.

[0011] Another important consideration is age, given that the degenerative processes associated with age are in part a result of unrepaired damage to macromolecules, produced by free radicals. 2-5% of inhaled oxygen is converted into toxic oxygen radicals, meaning that when an individual reaches 70 years of age he has produced more than 900 kg of oxygen radicals. Although these oxygen radicals are the basis of the aging process, they are also used by the cell for physiological processes, such as in the case of activated phagocytes which produce  $O_2$  to destroy bacteria or as chemical mediators (activation of the transcription factor (MF-kB)). [*Translator*: may have

meant “NF- $\kappa$ B”]

**[0012]** The antioxidant systems in the body must allow those necessary functions of oxygen radicals, but at the same time have to avoid their toxic effects.

**[0013]** Production of radicals is counteracted by an endogenous antioxidant system that makes use of several endogenous and exogenous compounds, among which are SOD, catalase, glutathione, and GSH-PX, as well as Vitamins A, C, and E.

**[0014]** Under oral illness and aging conditions, production of free radicals frequently exceeds the capacity to neutralize them and, as a consequence, many radicals are not neutralized and maintain a persistent bombardment of biologically important molecules, which is at least partially responsible for damage in those processes.

**[0015]** Melatonin is a very important component in the antioxidizing system of the body and can change the redox status of the cell.

**[0016]** When melatonin detoxifies OH, it becomes an indolyl cation radical which has a very low toxicity level, and this radical now purges the superoxide anion and becomes an N-acetyl-N-formyl-5-metoxkyurenamine.

**[0017]** This series of reactions makes melatonin an ideal purging agent, given that one molecule of melatonin purges two [molecules] of free radicals and to do this, melatonin does not require a specific receptor, acting directly on the cytosol and cell membrane. This means that its action is not excluded via a nuclear receptor that genomically modulates some antioxidant enzymes such as poly (ADP-ribose), polymerase, which repairs DNA, glutathione peroxidase and reductase, iNOS, and others.

**[0018]** Melatonin actions profoundly affect homeostasis, metabolism, the immune system, connective tissue maintenance and structural and muscular component maintenance. The last two, i.e., structural and muscular components, are responsible for elasticity and rigidity.

Melatonin regulates, directly and via calmodulin, tubulin synthesis for forming microtubules, the structure that forms the cell cytoskeleton and, therefore, melatonin actively participates in the maintenance of a correct cell structure and, consequently, in cell elasticity and/or rigidity.

[0019] Under normal conditions, a third of the melatonin circulating in the blood is excreted via saliva and through the mouth. There are data showing that this salival excretion of melatonin maintains suitable levels of the hormone to locally protect mouth tissue from the damage continually being received following or as a result of the mouth's physiological functions. As a result, a supply of exogenous melatonin to the mouth will be very useful in preventing oxidative damage and stimulating the local immune response.

[0020] Furthermore, if it is considered that levels of melatonin in the blood decrease drastically with age, the continuous supply of melatonin to the mouth in the form of toothpaste and/or mouthwash may prevent the onset of mouth diseases. The same is true for animals, where oral care will improve if an extra supply of melatonin is given in the feed.

[0021] The destructive effects produced on oral tissues in living beings by pathologies such as periodontopathies, among others, or as a result of surgical interventions in the oral cavity, are significant and affect, via the pertinent inflammatory process, both the mucosa and the bone tissue, and other neighboring tissues.

[0022] In these destructive processes, in which different kinds of germs are involved, oxidative stress, stemming from said inflammatory process, plays a vital role. The leukocytes play a vital role, in which a large number of free radicals, causing cell destruction, are released.

[0023] Medical treatments aimed at resolving these pathologies have concentrated on controlling the infection using antimicrobial drugs and controlling the inflammatory process, generally using non-steroidal anti-inflammatory drugs.

[0024] The idea of fighting the free radicals produced in the inflammatory response, to decrease cell destruction and allow a better regeneration of affected tissue, is combined with the attempt

the body already makes by using certain orally produced antioxidants such as ascorbic acid, albumin, and uric acid.

[0025] In this respect, it has been proposed that Vitamin A, Vitamin E, CoQ, among others, be used as topical and systemic antioxidants.

[0026] Both their antioxidizing capacity and the results obtained are much lower than the capacity of melatonin and its derivatives. Currently melatonin, a natural substance produced by the body, up to certain ages, in response to pathologies like this, has demonstrated a considerably higher power than those substances mentioned previously, entering the cell, even reaching its nucleus and protecting the cell from the free radicals produced during the inflammatory process, thereby averting its destruction.

[0027] The applicant is aware of the existence of Patents W 98/05298 and EP 820768, which use melatonin as an antioxidant in cosmetic products.

[0028] The applicant is also aware of the current existence of Patents WO 00/67708, US 5,665,332, DE 196 15 820, and GB 990,082, relating to toothpastes containing hormones.

[0029] Finally, patents are also known relating to pharmaceutical compounds administered orally or externally that include melatonin and that can be applied to animals in some cases, identified by numbers WO 96/08490, WO 92/06955, WO 95/26713, and WO 92/02207.

[0030] It is reiterated that all these aforementioned documents are part of the art prior to the invention described in this document. However, they can in no way be considered to affect its inventive step or its novelty.

## **Description of the invention**

[0031] Utilization of melatonin for human and animal oral hygiene as an active product is based on the use of melatonin, which is a natural hormone produced by all living organisms, from single cell beings to man and including plants.

[0032] Consequently, melatonin is a natural, not synthetic, product. However, melatonin in a pure form can be purchased from regular suppliers of chemical products, which is the form in which it is purchased for research.

[0033] As previously mentioned, different research has demonstrated that it is an excellent natural antioxidant with immunomodulatory actions. Based on that, this invention uses the properties of melatonin to use it as an oral protector. For this purpose, melatonin is introduced into the composition of toothpastes and into mouthwashes. It will also be used for the same purposes in animals by including it as a component of animal feed.

#### **Preferred embodiment of the invention**

[0034] Utilization of melatonin for human and animal oral hygiene as an active product and in particular in preparing toothpastes, using both hydrophilic and hydrophobic bases or excipients that can be used in the preparation of a toothpaste and/or a mouthwash in the master formulation and in industrial preparation. For that, melatonin will be used in a proportion of 0.1% to 5% in said toothpastes and/or mouthwashes.

[0035] For the preparation of animal feeds, melatonin will be added in a proportion of 0.1% to 5% in said feeds.

[0036] The melatonin may be degraded by autooxidation or action of microbial enzymes. To avoid autooxidation of the melatonin, each of the previously mentioned preparations will include the most suitable antioxidant for each case.

[0037] The antioxidant will be active at a low concentration and in a wide pH range, soluble in the medium used and, if possible, colorless, thermostable and, of course, non-toxic, non-



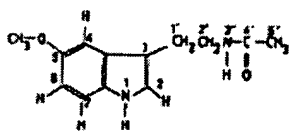
irritating, and non-volatile.

[0038] Among those commonly used in formulation are sodium sulphite and bisulphate, ascorbic acid, hydroquinone, nipagin, vitamin E, vitamin A, etc.

[0039] Its effectiveness can be increased with the use of synergic-effect substances such as citric and tartaric acids, as well as EDTA.

[0040] A preservative must be added to avoid degradation by microbial contamination. The preservative used will be non-toxic, chemically stable, and compatible with melatonin. Among these, benzoic acid, salicylic acid, sorbic acid, and essential oils will be used.

The specific formula of this invention follows.

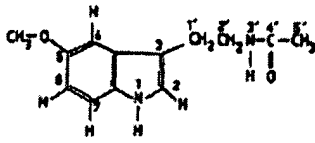


Melatonin:

N-acetyl-5-methoxytryptamine

## CLAIMS

1. Use of melatonin for human and animal oral hygiene as an active product of those intended to be used in toothpastes, mouthwashes, or animal feed,  
**characterized** in that the preparation of the toothpaste includes hydrophilic and hydrophobic bases or excipients capable of being used in the preparation of a toothpaste and/or mouthwash in master formulations and in industrial preparations, melatonin being incorporated in a proportion of 0.1% to 5% in toothpastes and/or mouthwashes, as well as in animal feed.
2. Use of melatonin for human and animal oral hygiene as an active product, as recited in the first claim,  
**characterized** in that, to prevent autooxidation of the melatonin, each of the preparations includes an antioxidant which is active at a low concentration and in a wide pH range, soluble in the medium used, colorless, thermostable, non-toxic, non-irritating, and non-volatile, such as sodium sulphite and bisulphate, ascorbic acid, hydroquinone, nipagin, vitamin E, vitamin A, and the effectiveness can be increased with the use of synergic-effect substances such as citric and tartaric acids, as well as EDTA.
3. Use of melatonin for human and animal oral hygiene as an active product ,as recited in the previous claims,  
**characterized** in that, to avoid degradation by microbial contamination, a non-toxic, chemically stable, melatonin-compatible preservative, such as benzoic acid, salicylic acid, sorbic acid, and essential oils, is added.
4. Use of melatonin for human and animal oral hygiene as an active product, as recited in the previous claims,  
**characterized** in that the general formula of the melatonin as an active product is:



Melatonin:

N-acetyl-5-methoxytryptamine

[symbol] SPANISH PATENT AND TRADEMARK OFFICE  SPAIN	11) <b>ES 2 209 649</b> 21) Application No. 200202810 22) Application submission date: <b>12/9/2002</b> 32) Priority date:
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# REPORT ON PRIOR ART

51) **Int. Cl.<sup>7</sup>**: A61K 31/4045, 7/16, 38/22, A23K 1/165

## RELEVANT DOCUMENTS

Category	Documents cited	Claims affected
A	WO 02076452 A (POOGER PROPERTIES LIMITED) 10/3/2002	1
A	JP 61-212512 A (SHISEIDO CO LTD.) 9/20/1986 (abstract) World Patent Index [on line] [Retrieved on 2/24/2004] Retrieved from: WPI EPO Database	1
A	WO 9805298A (UNIVERSIDAD DE GRANADA) 2/12/1998	1
A	ES 2131468 (UNIVERSIDAD DE OVIEDO) 7/16/1999	1
<b>Category of the documents cited</b> X: of particular relevance Y: of particular relevance combined with another/others of the same category A: reflects prior art		O: refers to unwritten disclosure P: published between the priority date and the application submission date E: previous document, but published after the application submission date

<b>This report has been made</b> <input checked="" type="checkbox"/> For all claims		<input type="checkbox"/> for claims no.:
<b>Date of report</b> 5/14/2004	<b>Examiner</b> A. Amaro Roldán	<b>Page</b> 1/1